	L #	Hits	Search Text	DBs	Time Stamp
1	L1	38	suramin.clm.	USPAT	2003/11/13 12:59
2	L2	17068	refractory.clm.	USPAT	2003/11/13 13:15
3	L3	818	egfr or her1	USPAT	2003/11/13 13:16
4	L4	0	2 and 3	USPAT	2003/11/13 13:16
5	L5	19185	metasta$4	USPAT	2003/11/13 13:16
6	L6	390	3 and 5	USPAT	2003/11/13 13:16
7	L7	4591	435/7.1.ccls.	USPAT	2003/11/13 13:17
8	L8	19	6 and 7	USPAT	2003/11/13 13:29
9	L9	2451	prosta$4.clm.	USPAT	2003/11/13 13:29
10	L10	51	7 and 9 and (2 or 5)	USPAT	2003/11/13 13:37
11	L11	91	egfr.clm. or her-1.clm. or p180.clm. or erbb1.clm.	USPAT	2003/11/13 13:40
12	L12	2854	antagonist.clm.	USPAT	2003/11/13 13:38
13	L13	2	11 and 12	USPAT	2003/11/13 13:40
14	L14	882	suramin	USPAT	2003/11/13 13:40
15	L15	1	11 and 14	USPAT	2003/11/13 13:40

L4 ANSWER 1 OF 48 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:855388 CAPLUS
TITLE: Treatment of ***refractory*** human tumors with epidermal growth factor receptor and ***HER1*** mitogenic ligand (EGFRML) antagonists
INVENTOR(S): Pieczenik, George
PATENT ASSIGNEE(S): George Pieczenik, USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003202973	A1	20031030	US 2002-63930	20020527

PRIORITY APPLN. INFO.: US 2002-319212P P 20020429
US 2002-319269P P 20020526
AB A method of inhibiting the growth of ***refractory*** tumors that are stimulated by mitogenic ligands of epidermal growth factor receptor in human patients, comprising treating the human patients with an effective amt. of a mitogenic ligand antagonist.

L4 ANSWER 2 OF 48 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003481664 IN-PROCESS
DOCUMENT NUMBER: 22921930 PubMed ID: 14560030
TITLE: Molecular mechanism for a role of SHP2 in epidermal growth factor receptor signaling.
AUTHOR: Agazie Yehenew M; Hayman Michael J
CORPORATE SOURCE: Department of Molecular Genetics and Microbiology, Health Sciences Center, Stony Brook University, Stony Brook, New York 11794-5222, USA.
CONTRACT NUMBER: CA28146 (NCI)
CA42573 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2003 Nov) 23 (21) 7875-86.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031016
Last Updated on STN: 20031024
AB The Src homology 2-containing phosphotyrosine phosphatase (SHP2) is primarily a positive effector of receptor tyrosine kinase signaling. However, the molecular mechanism by which SHP2 effects its biological function is unknown. In this report, we provide evidence that defines the molecular mechanism and site of action of SHP2 in the epidermal growth factor-induced mitogenic pathway. We demonstrate that SHP2 acts upstream of Ras and functions by increasing the half-life of activated Ras (GTP-Ras) in the cell by interfering with the process of Ras inactivation catalyzed by Ras GTPase-activating protein (RasGAP). It does so by inhibition of tyrosine phosphorylation-dependent translocation of RasGAP to the plasma membrane, to its substrate (GTP-Ras) microdomain. Inhibition is achieved through the dephosphorylation of RasGAP binding sites at the level of the plasma membrane. We have identified Tyr992 of the epidermal growth factor receptor (***EGFR***) to be one such site, since its mutation to Phe renders the ***EGFR*** ***refractory*** to the effect of dominant-negative SHP2. To our knowledge, this is the first report to outline the site and molecular mechanism of action of SHP2 in ***EGFR*** signaling, which may also serve as a model to describe its role in other receptor tyrosine kinase signaling pathways.

L4 ANSWER 3 OF 48 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003466095 IN-PROCESS
DOCUMENT NUMBER: 22890082 PubMed ID: 14528322

TITLE: Conditionally replicative adenovirus expressing a targeting adapter molecule exhibits enhanced oncolytic potency on CAR-deficient tumors.
AUTHOR: van Beusechem V W; Mastenbroek D C J; van den Doel P B; Lamfers M L M; Grill J; Wurdinger T; Haisma H J; Pinedo H M; Gerritsen W R
CORPORATE SOURCE: Division of Gene Therapy, Department of Medical Oncology, The Netherlands.
SOURCE: GENE THERAPY, (2003 Nov) 10 (23) 1982-91.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031008
Last Updated on STN: 20031023
AB Conditionally replicative adenoviruses (CRAds) are potentially useful agents for anticancer virotherapy approaches. However, lack of coxsackievirus and adenovirus receptor (CAR) expression on many primary tumor cells limits the oncolytic potency of CRAds. This makes the concept of targeting, that is, redirecting infection via CAR-independent entry pathways, relevant for CRAd development. Bispecific adapter molecules constitute highly versatile means for adenovirus targeting. Here, we constructed a CRAd with the Delta24 E1A mutation that produces a bispecific single-chain antibody directed towards the adenovirus fiber knob and the epidermal growth factor receptor (***EGFR***). This ***EGFR*** -targeted CRAd exhibited increased infection efficiency and oncolytic replication on CAR-deficient cancer cells and augmented lateral spread in CAR-deficient 3-D tumor spheroids in vitro. When compared to its parent control with native tropism, the new CRAd exhibited similar cytotoxicity on CAR-positive cancer cells, but up to 1000-fold enhanced oncolytic potency on CAR-deficient, ***EGFR*** -positive cancer cells. In addition, ***EGFR*** -targeted CRAd killed primary human CAR-deficient brain tumor specimens that were ***refractory*** to the parent control virus. We conclude, therefore, that CRAds expressing bispecific targeting adapter molecules are promising agents for cancer treatment. Their use is likely to result in enhanced oncolytic replication in cancerous tissues and thus in more effective tumor regression.

L4 ANSWER 4 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2003221652 MEDLINE
DOCUMENT NUMBER: 22628215 PubMed ID: 12743152
TITLE: Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck.
AUTHOR: Cohen Ezra E W; Rosen Fred; Stadler Walter M; Recant Wendy; Stenson Kerstin; Huo Dezheng; Vokes Everett E
CORPORATE SOURCE: Section of Hematology/Oncology, Department of Medicine, University of Chicago, 5841 S Maryland Ave, MC 2115, Chicago, IL 60637-1470, USA.. ecohen@medicine.bsd.uchicago.edu
CONTRACT NUMBER: N01-CM-17102 (NCI)
P30 CA14599 (NCI)
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (2003 May 15) 21 (10) 1980-7.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030514
Last Updated on STN: 20030528
Entered Medline: 20030527
AB PURPOSE: The epidermal growth factor receptor (***EGFR***) is a mediator of squamous cell carcinoma of the head and neck (SCCHN)

development. ZD1839 is an orally active, selective ***EGFR*** tyrosine kinase inhibitor. This phase II study sought to explore the activity, toxicity, and pharmacodynamics of ZD1839 in SCCHN. PATIENTS AND METHODS: Patients with recurrent or metastatic SCCHN were enrolled through the University of Chicago Phase II Consortium. Patients were allowed no more than one prior therapy for recurrent or metastatic disease and were treated with single-agent ZD1839 500 mg/d. Patient tumor biopsies were obtained and stained immunohistochemically for ***EGFR*** , extracellular signal-regulated kinase 1 (ERK1), and phosphorylated ERK1 (p-ERK). Study end points included response rate, time to progression, median survival, and inhibition of p-ERK. RESULTS: Fifty-two patients were enrolled (40 male and 12 female) with a median age of 59 years (range, 34 to 84 years). Fourteen patients received ZD1839 through a feeding tube. Half the cohort received ZD1839 as second-line therapy. Forty-seven patients were assessable for response, with an observed response rate of 10.6% and a disease control rate of 53%. Median time to progression and survival were 3.4 and 8.1 months, respectively. The only grade 3 toxicity encountered was diarrhea in three patients. Performance status and development of skin toxicity were found to be strong predictors of response, progression, and survival. Ten biopsy samples were assessable and revealed no significant change in ***EGFR*** or p-ERK expression with ZD1839 therapy. CONCLUSION: ZD1839 has single-agent activity and is well tolerated in ***refractory*** SCCHN. In contrast to other reports, development of skin toxicity was a statistically significant predictor of response and improved outcome.

L4 ANSWER 5 OF 48 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003269547 IN-PROCESS
DOCUMENT NUMBER: 22680488 PubMed ID: 12796025
TITLE: Expression of KIT and epidermal growth factor receptor in chemotherapy ***refractory*** non-seminomatous germ-cell tumors.
AUTHOR: Madani A; Kemmer K; Sweeney C; Corless C; Ulbright T; Heinrich M; Einhorn L
CORPORATE SOURCE: Division of Hematology and Oncology, and Department of Pathology, Indiana University Medical Center, Indianapolis, IN 46202, USA.. amadani@iupui.edu
CONTRACT NUMBER: P01 CA74295 (NCI)
SOURCE: ANNALS OF ONCOLOGY, (2003 Jun) 14 (6) 873-80. Journal code: 9007735. ISSN: 0923-7534.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030611
Last Updated on STN: 20030722
AB BACKGROUND: The majority of patients with germ-cell tumors (GCTs) are curable with standard therapy. The molecular differences between curable and incurable disease are unknown. We have studied the expression of KIT and the epidermal growth factor receptor (***EGFR***) to determine their incidence in chemorefractory disease. PATIENTS AND METHODS: We retrospectively analyzed 23 patients with chemorefractory non-seminomatous GCTs (15 late relapse and eight transformed teratomas). None of these 23 patients were cured by their initial chemotherapy and/or surgery. Immunohistochemical analysis of KIT and ***EGFR*** was performed on the most recently available specimen from a metastatic site. PCR amplimers of KIT exon 17 were screened for mutations by a combination of denaturing high-performance liquid chromatography and direct sequencing. RESULTS: KIT was expressed (>/=10% of the tumor displaying membranous or cytoplasmic staining) in 11 of 23 GCT patients [48%; 95% confidence interval (CI) 26% to 68%]. There were no activating KIT mutations in the phosphoryltransferase domain (exon 17) in 21 patients analyzed. ***EGFR*** was expressed (1+ to 3+) in 15 of 23 GCT patients (65%; 95% CI 41% to 82%). CONCLUSIONS: KIT and ***EGFR*** are expressed in a significant proportion of ***refractory*** GCTs. The significance of these findings will be determined by ongoing clinical trials.

L4 ANSWER 6 OF 48 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003483408 MEDLINE
DOCUMENT NUMBER: 22923597 PubMed ID: 14562277
TITLE: Epidermal growth factor receptor expression in follicular dendritic cells: a shared feature of follicular dendritic cell sarcoma and Castleman's disease.
AUTHOR: Sun Xiaoping; Chang Kong-Chao; Abruzzo Lynne V; Lai Raymond; Younes Anas; Jones Dan
CORPORATE SOURCE: Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.
CONTRACT NUMBER: CA16672 (NCI)
SOURCE: HUMAN PATHOLOGY, (2003 Sep) 34 (9) 835-40.
Journal code: 9421547. ISSN: 0046-8177.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20031017
Last Updated on STN: 20031029
Entered Medline: 20031028
AB The factors regulating the growth of follicular dendritic cell (FDC) sarcoma are currently unknown. Using cDNA microarray analysis, we found that the epidermal growth factor receptor (***EGFR***) is expressed in FDC sarcoma. We immunohistochemically examined the expression of ***EGFR*** in a larger series of FDC sarcomas and in nonneoplastic FDCs. This included 8 cases of FDC sarcoma, 12 cases of hyaline vascular Castleman's disease (CD), 5 cases of human herpesvirus 8 (HHV8)-positive plasma cell CD, 7 cases of HHV8-negative plasma cell CD, 13 cases of reactive lymph nodes, 3 cases of reactive tonsils, 10 cases of follicular lymphoma, 6 cases of nodular mantle cell lymphoma, and 6 cases of angioimmunoblastic T-cell lymphoma. ***EGFR*** was expressed in tumor cells in 7 of 8 cases (88%) of FDC sarcoma (strongly in 4 cases and moderately in 3 cases). The single ***EGFR*** -negative case had an anaplastic appearance and a more aggressive clinical behavior. ***EGFR*** was also expressed by FDC in all types of CD (strongly in 4 cases, moderately in 16 cases, and weakly in 4 cases). Immunostaining results were negative or only weakly positive for ***EGFR*** in FDC of reactive lymph nodes and tonsils, and in the FDC networks of follicular lymphoma, mantle cell lymphoma, and angioimmunoblastic lymphoma. The up-regulation of ***EGFR*** in FDC of CD was paralleled by an increase in ***EGFR*** expression in the surrounding perifollicular fibroblastic reticulum cells suggesting coordinate regulation. These findings identify a differentially expressed growth regulatory receptor common to both FDC sarcoma and CD, identifying a target for possible therapy in unresectable or ***refractory*** cases.

L4 ANSWER 7 OF 48 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003400985 IN-PROCESS
DOCUMENT NUMBER: 22820616 PubMed ID: 12939468
TITLE: Growth factor receptor expression varies among high-grade gliomas and normal brain: epidermal growth factor receptor has excellent properties for interstitial fusion protein therapy.
AUTHOR: Liu Tie Fu; Tatter Stephen B; Willingham Mark C; Yang Mitchell; Hu Jennifer J; Frankel Arthur E
CORPORATE SOURCE: Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157, USA.
SOURCE: Mol Cancer Ther, (2003 Aug) 2 (8) 783-7.
Journal code: 101132535. ISSN: 1535-7163.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030827
Last Updated on STN: 20030828
AB Convection-enhanced delivery of fusion proteins is a novel therapeutic

approach for patients with relapsed or ***refractory*** high-grade gliomas. Multiple different fusion proteins have been produced that target different receptors on brain tumor cells. The sensitivity of different gliomas to fusion proteins has been shown to depend in part on the expression of the target receptor. We undertook a comparative study of the presence of the epidermal growth factor receptor (***EGFR***), interleukin-13 receptor (IL13R), interleukin-4 receptor (IL4R), and transferrin receptor (TfR) determined by immunofluorescence microscopy among fresh frozen tumor samples from 38 patients with high-grade gliomas (glioblastoma multiforme or anaplastic astrocytoma). The frequency of high receptor expression was 32 of 38 (84%) for ***EGFR*** , 30 of 38 (79%) for IL13R, 25 of 38 (66%) for TfR, and 17 of 38 (45%) for IL4R. Reactivity of normal brain endothelium was observed for TfR, and reactivity of normal brain astrocytes was observed for IL4R. Because of cross-reactivity of interleukin-13 with the IL4R-IL13Ralpha1 receptor, we infer reactivity of interleukin-13 with normal astrocytes. In contrast, ***EGFR*** was not observed in normal brain. A number of patients (10 of 38 patients) showed unequal expression of ***EGFR*** and IL13R. Thus, some patients may benefit more from interstitial therapy with an ***EGFR*** -directed fusion protein than from therapy with an IL13R-directed fusion protein and vice versa. The safety profile may be improved with an agent directed to ***EGFR*** versus agents directed to TfR, IL4R, or IL13R. Design of clinical trials of fusion proteins in patients with brain tumors may be enhanced by inclusion of relevant receptor density measurements.

L4 ANSWER 8 OF 48 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2003367675 MEDLINE
DOCUMENT NUMBER: 22783474 PubMed ID: 12901223
TITLE: Epidermal growth factor receptor inhibitors: an update on their development as cancer therapeutics.
AUTHOR: Seymour Lesley
CORPORATE SOURCE: National Cancer Institute of Canada Clinical Trials Group, Queens University, Kingston, Ontario, K7L3N6, Canada..
lseymour@ctg.queensu.ca
SOURCE: Curr Opin Investig Drugs, (2003 Jun) 4 (6) 658-66. Ref: 133
Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030807
Last Updated on STN: 20030910
Entered Medline: 20030909
AB Therapeutic agents targeting the epidermal growth factor receptor (***EGFR***) have recently been approved for use in patients based on the results of large-scale phase II studies involving patients with advanced ***refractory*** non-small-cell lung cancer (NSCLC). Disappointingly, results from phase III trials of gefitinib in combination with standard chemotherapy regimens for the treatment of NSCLC were negative. While results from phase III trials with other agents such as erlotinib and cetuximab will be reported in the next 12 to 18 months, the early results raise a number of questions regarding the development of these agents, including patient selection (e.g., disease, stage, prior therapy, ***EGFR*** or other biomarker expression) and combinations with standard treatment regimens as well as hormonal agents, radiation or other novel agents which will require further elucidation. Early data suggest a number of potential roles for these agents in the modulation of resistance and in combination with other inhibitors of signal transduction.

L4 ANSWER 9 OF 48 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2003296063 IN-PROCESS
DOCUMENT NUMBER: 22707576 PubMed ID: 12824893

TITLE: A report of two bronchioloalveolar carcinoma cases which were rapidly improved by treatment with the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 ("Iressa"(1)).
AUTHOR: Yano Seiji; Kanematsu Takanori; Miki Toyokazu; Aono Yoshinori; Azuma Masahiko; Yamamoto Akihiko; Uehara Hisanori; Sone Saburo
CORPORATE SOURCE: Department of Internal Medicine, University of Tokushima School of Medicine, Tokushima 770-8503, Japan.. manae@clin.med.tokushima-u.ac.jp
SOURCE: Cancer Sci, (2003 May) 94 (5) 453-8.
Journal code: 101168776. ISSN: 1347-9032.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030626
Last Updated on STN: 20030626
AB Bronchioloalveolar carcinoma (BAC), a form of pulmonary adenocarcinoma, presents unique clinical features, such as endobronchial spread and bronchorrhea in advanced stages. The prognosis for BAC patients in advanced stages is poor, as is the case for patients with other non-small-cell lung cancer (NSCLC) types, because of low susceptibility to conventional chemotherapy. Recently, an orally active, selective epidermal growth factor receptor (***EGFR***) tyrosine kinase inhibitor (***EGFR*** -TKI), ZD1839 ("Iressa"), has been investigated in phase II clinical studies (IDEAL 1 and IDEAL 2) as monotherapy against chemotherapy- ***refractory*** NSCLC, and provided clinically significant antitumor activity. In this study, we examined the therapeutic efficiency of ZD1839 in chemotherapy- ***refractory*** BAC patients with bronchorrhea. Two female BAC patients with bronchorrhea were treated once daily with ZD1839 (250 mg/day). In both cases, serous sputum production was dramatically reduced within 3 days of starting the treatment, and hypoxia and radiographic signs of bilateral lung consolidation were visibly improved within 7 days. Following more than 8 months of treatment, no evidence of recurrence or severe adverse events has been observed. These results suggest that this selective ***EGFR*** -TKI, ZD1839, may be a powerful agent for treatment of chemotherapy- ***refractory*** BAC patients with bronchorrhea.

L4 ANSWER 10 OF 48 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2003425313 IN-PROCESS
DOCUMENT NUMBER: 22846391 PubMed ID: 12965607
TITLE: The switch from DNA repair to apoptosis: discovery of a ***refractory*** period for radiation-induced ***EGFR*** -MAPK signaling following irradiation.
AUTHOR: Hagan M P; Yacoub A; Dent P
CORPORATE SOURCE: Department of Radiation Oncology, Virginia Commonwealth University, Richmond, VA, USA.
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (2003 Oct 1) 57 (2 Suppl) S294-5.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030911
Last Updated on STN: 20030911

L4 ANSWER 11 OF 48 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2002741878 MEDLINE
DOCUMENT NUMBER: 22393498 PubMed ID: 12414812
TITLE: Aplidin induces apoptosis in human cancer cells via glutathione depletion and sustained activation of the epidermal growth factor receptor, Src, JNK, and p38 MAPK.
AUTHOR: Cuadrado Ana; Garcia-Fernandez Luis F; Gonzalez Laura; Suarez Yajaira; Losada Alejandro; Alcaide Victoria;

Martinez Teresa; Fernandez-Sousa Jose Maria;
Sanchez-Puelles Jose Maria; Munoz Alberto
CORPORATE SOURCE: Drug Discovery Department, PharmaMar S. A., Tres Cantos, E-28760 Madrid, Spain.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Jan 3) 278 (1) 241-50.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021231
Last Updated on STN: 20030211
Entered Medline: 20030210

AB We report that Aplidin, a novel antitumor agent of marine origin presently undergoing Phase II clinical trials, induced growth arrest and apoptosis in human MDA-MB-231 breast cancer cells at nanomolar concentrations. Aplidin induced a specific cellular stress response program, including sustained activation of the epidermal growth factor receptor (***EGFR***), the non-receptor protein-tyrosine kinase Src, and the serine/threonine kinases JNK and p38 MAPK. Aplidin-induced apoptosis was only partially blocked by the general caspase inhibitor benzyloxycarbonyl-VAD-fluoromethyl ketone and was also sensitive to AG1478 (an ***EGFR*** inhibitor), PP2 (an Src inhibitor), and SB203580 (an inhibitor of JNK and p38 MAPK) in MDA-MB-231 cells. Supporting a role for ***EGFR*** in Aplidin action, ***EGFR*** -deficient mouse embryo fibroblasts underwent apoptosis upon treatment more slowly than wild-type ***EGFR*** fibroblasts and also showed delayed JNK and reduced p38 MAPK activation. N-Acetylcysteine and ebselen (but not other antioxidants such as diphenyleneiodonium, Tiron, catalase, ascorbic acid, and vitamin E) reduced ***EGFR*** activation by Aplidin. N-Acetylcysteine and PP2 also partially inhibited JNK and p38 MAPK activation. The intracellular level of GSH affected Aplidin action; pretreatment of cells with GSH or N-acetylcysteine inhibited, whereas GSH depletion caused, hyperinduction of ***EGFR*** , Src, JNK, and p38 MAPK. Remarkably, Aplidin also induced apoptosis and activated ***EGFR*** , JNK, and p38 MAPK in two cell lines (A-498 and ACHN) derived from human renal cancer, a neoplasia that is highly ***refractory*** to chemotherapy. These data provide a molecular basis for the anticancer activity of Aplidin.

L4 ANSWER 12 OF 48 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2003071176 MEDLINE
DOCUMENT NUMBER: 22469099 PubMed ID: 12580917
TITLE: The role of the epidermal growth factor receptor in sustaining neutrophil inflammation in severe asthma.
AUTHOR: Hamilton L M; Torres-Lozano C; Puddicombe S M; Richter A; Kimber I; Dearman R J; Vrugt B; Aalbers R; Holgate S T; Djukanovic R; Wilson S J; Davies D E
CORPORATE SOURCE: Division of Infection, Inflammation & Repair, School of Medicine, University of Southampton, UK.
SOURCE: CLINICAL AND EXPERIMENTAL ALLERGY, (2003 Feb) 33 (2) 233-40.
Journal code: 8906443. ISSN: 0954-7894.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030214
Last Updated on STN: 20030416
Entered Medline: 20030414

AB BACKGROUND: The extent of epithelial injury in asthma is reflected by expression of the epidermal growth factor receptor (***EGFR***), which is increased in proportion to disease severity and is corticosteroid ***refractory*** . Although the ***EGFR*** is involved in epithelial growth and differentiation, it is unknown whether it also contributes to

[redacted]

the inflammatory response in asthma. OBJECTIVES: Because severe asthma is characterized by neutrophilic inflammation, we investigated the relationship between ***EGFR*** activation and production of IL-8 and macrophage inhibitory protein-1 alpha (MIP-1alpha) using in vitro culture models and examined the association between epithelial expression of IL-8 and ***EGFR*** in bronchial biopsies from asthmatic subjects. METHODS: H292 or primary bronchial epithelial cells were exposed to EGF or H2O2 to achieve ligand-dependent and ligand-independent ***EGFR*** activation; IL-8 mRNA was measured by real-time PCR and IL-8 and MIP-1alpha protein measured by enzyme-linked immunosorbent assay (ELISA). Epithelial IL-8 and ***EGFR*** expression in bronchial biopsies from asthmatic subjects was examined by immunohistochemistry and quantified by image analysis. RESULTS: Using H292 cells, EGF and H2O2 increased IL-8 gene expression and release and this was completely suppressed by the ***EGFR*** -selective tyrosine kinase inhibitor, AG1478, but only partially by dexamethasone. MIP-1alpha release was not stimulated by EGF, whereas H2O2 caused a 1.8-fold increase and this was insensitive to AG1478. EGF also significantly stimulated IL-8 release from asthmatic or normal primary epithelial cell cultures established from bronchial brushings. In bronchial biopsies, epithelial IL-8, MIP-1alpha, ***EGFR*** and submucosal neutrophils were all significantly increased in severe compared to mild disease and there was a strong correlation between ***EGFR*** and IL-8 expression ($r = 0.70$, $P < 0.001$). CONCLUSIONS: These results suggest that in severe asthma, epithelial damage has the potential to contribute to neutrophilic inflammation through enhanced production of IL-8 via ***EGFR*** - dependent mechanisms.

L4 ANSWER 13 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:232330 BIOSIS
DOCUMENT NUMBER: PREV200300232330
TITLE: Expression patterns of potential therapeutic targets in prostate cancer.
AUTHOR(S): Zellweger, Tobias [Reprint Author]; Ninck, Christoph; Mirlacher, Martina; Koivisto, Pasi A.; Bloch, Michael; Mihatsch, Michael J.; Gasser, Thomas C.; Bubendorf, Lukas
CORPORATE SOURCE: Liestal, Switzerland
SOURCE: Journal of Urology, (April 2003) Vol. 169, No. 4 Supplement, pp. 213. print.
Meeting Info.: 98th Annual Meeting of the American Urological Association (AUA). Chicago, IL, USA. April 26-May 02, 2003. American Urological Association.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 May 2003
Last Updated on STN: 14 May 2003

L4 ANSWER 14 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:442116 BIOSIS
DOCUMENT NUMBER: PREV200300442116
TITLE: Antagonistic effects resulting from the dual targeting of ***EGFR*** and HER2 on hormone- ***refractory*** prostate cancer cells.
AUTHOR(S): Formento, Patricia [Reprint Author]; Fischel, Jean-Louis [Reprint Author]; Hannoun-Levi, Jean-Michel [Reprint Author]; Etienne, Marie-Christine [Reprint Author]; Ilc, Karine [Reprint Author]; Formento, Jean-Louis [Reprint Author]; Magne, Nicolas [Reprint Author]; Milano, Gerard [Reprint Author]
CORPORATE SOURCE: Centre Antoine Lacassagne, Nice, France
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 201-202. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.

ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

L4 ANSWER 15 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:442113 BIOSIS
DOCUMENT NUMBER: PREV200300442113
TITLE: Gefitinib ('Iressa', ZD1839) and a second generation antisense targeting murine double minute 2 (Mdm2) synergistically inhibit tumor growth and angiogenesis in hormone- ***refractory*** prostate cancer cells.
AUTHOR(S): Bianco, Roberto [Reprint Author]; Caputo, Roberta [Reprint Author]; Caputo, Rosa [Reprint Author]; Damiano, Vincenzo [Reprint Author]; Melisi, Davide [Reprint Author]; Bianco, A. Raffaele [Reprint Author]; Ciardiello, Fortunato [Reprint Author]; Tortora, Giampaolo [Reprint Author]
CORPORATE SOURCE: Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 201. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

L4 ANSWER 16 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:232192 BIOSIS
DOCUMENT NUMBER: PREV200300232192
TITLE: COX-2, angiogenesis and bcl-2 as prognostic factors in prostate cancer: Their correlation with ***EGFR*** expression, disease relapse and progression to androgen-indipendence.
AUTHOR(S): Autorino, Riccardo [Reprint Author]; Di Lorenzo, Giuseppe [Reprint Author]; D'Armiento, Francesco [Reprint Author]; Ciardiello, Fortunato [Reprint Author]; De Placido, Sabino [Reprint Author]; Bianco, Angelo Raffaele [Reprint Author]; D'Armiento, Massimo [Reprint Author]
CORPORATE SOURCE: Naples, Italy
SOURCE: Journal of Urology, (April 2003) Vol. 169, No. 4 Supplement, pp. 164-165. print.
Meeting Info.: 98th Annual Meeting of the American Urological Association (AUA). Chicago, IL, USA. April 26-May 02, 2003. American Urological Association.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 May 2003
Last Updated on STN: 14 May 2003

L4 ANSWER 17 OF 48 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2003324058 MEDLINE
DOCUMENT NUMBER: 22737906 PubMed ID: 12853203
TITLE: Targeting epidermal growth factor receptor--are we missing the mark?.
AUTHOR: Dancey Janet E; Freidlin Boris
CORPORATE SOURCE: Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD 20892, USA.

SOURCE: LANCET, (2003 Jul 5) 362 (9377) 62-4. Ref: 20
Journal code: 2985213R. ISSN: 1474-547X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030711
Last Updated on STN: 20030724
Entered Medline: 20030723

AB CONTEXT: Aberrant signalling through the epidermal growth factor receptor (***EGFR***) is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis, and angiogenesis. The high frequency of abnormalities in ***EGFR*** signalling in human carcinomas and gliomas and laboratory studies showing that inhibition of EGFRcan impair tumour growth means that ***EGFR*** is an attractive target for the development of cancer therapeutics. Among the classes of agents targeting ***EGFR*** in clinical development are monoclonal antibodies against the extracellular ligand-binding domain of the receptor, and small molecules that inhibit activation of the receptor tyrosine kinase. Although there are pharmacological and mechanistic differences between the two classes of inhibitor, preclinical studies suggest they both inhibit cell proliferation and have additive or synergistic cytotoxicity with standard therapies. Results from early clinical trials indicate that these agents are well tolerated and have anti-tumour activity. STARTING POINT: In May, 2003, the Australian Therapeutic Goods Administration and the US Food and Drug Administration approved the ***EGFR*** inhibitor gefitinib (ZD1839, Iressa) for the treatment of patients with advanced non-small-cell lung cancer (NSCLC) previously treated with chemotherapy. The US approval was based on results of a phase 2 study of 216 patients with NSCLC, including 142 patients with ***refractory*** disease. In this subgroup, the response rate was about 10%. The approval of the drug was granted despite negative results from two randomised controlled trials in over 2000 previously untreated patients with NSCLC, which showed no benefit in survival, objective tumour response, or time to progression when gefitinib was added to chemotherapy. WHERE NEXT? Research is needed to identify and validate predictive factors that can be used to select patients with disease likely to respond to ***EGFR*** inhibitors, and to elucidate the mechanism of interaction of these agents with standard therapies and other molecularly targeted agents. Appropriately designed clinical trials are required to define the optimum dose, schedule, and sequence for these agents in combination with conventional therapies and other targeted agents.

L4 ANSWER 18 OF 48 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2003227975 MEDLINE
DOCUMENT NUMBER: 22634647 PubMed ID: 12749703
TITLE: Rat brain tumor models to assess the efficacy of boron neutron capture therapy: a critical evaluation.
AUTHOR: Barth Rolf F; Yang Weilian; Coderre Jeffrey A
CORPORATE SOURCE: Department of Pathology, The Ohio State University, Columbus, OH 43210, USA.. barth.1@osu.edu
SOURCE: JOURNAL OF NEURO-ONCOLOGY, (2003 Mar-Apr) 62 (1-2) 61-74.
Ref: 84
Journal code: 8309335. ISSN: 0167-594X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030517
Last Updated on STN: 20030621

[redacted]

Entered Medline: 20030620

AB Development of any therapeutic modality can be facilitated by the use of the appropriate animal models to assess its efficacy. This report primarily will focus on our studies using the F98 and 9L rat glioma models to evaluate the effectiveness of boron neutron capture therapy (BNCT) of brain tumors. Following intracerebral implantation the biological behavior of each tumor resembles that of human high grade gliomas in a number of ways. In both models, glioma cells were implanted intracerebrally into syngeneic Fischer rats and approximately 10-14 days later BNCT was initiated at the Brookhaven National Laboratory Medical Research Reactor. Two low molecular weight (M(r) < 210Da) 10B-containing drugs, boronophenylalanine (BPA) and/or sodium borocaptate (BSH) were used as capture agents, either alone or in combination with each other. The 9L gliosarcoma, which has been difficult to cure by means of either chemo- or radiotherapy alone, was readily curable by BNCT. The best survival data were obtained using BPA at a dose of 1200 mg/kg (64.8mg 10B), administered intraperitoneally (i.p.), with a 100% survival rate at 8 months. In contrast, the F98 glioma has been ***refractory*** to all therapeutic modalities. Tumor bearing animals, which had received 500 mg/kg (27 mg 10B) of BPA, or an equivalent amount of BSH i.v., had mean survival time (MST) of 37 and 33 days, respectively, compared to 29 days for irradiated controls. The best survival data with the F98 glioma model were obtained using BPA + BSH in combination, administered intra-arterially via the internal carotid artery (i.c.) with hyperosmotic mannitol induced blood-brain barrier disruption (BBB-D). The MST was 140 days with a cure rate of 25%, compared to a MST of 73 days with a 5% cure rate without BBB-D, and 41 days following i.v. administration of both drugs. A modest but significant increase in MST also was observed in rats that received intracarotid (i.c.) BPA in combination with Cereport (RMP-7), which produced a pharmacologically mediated opening of the BBB. Studies also have been carried out with the F98 glioma to determine whether an X-ray boost could enhance the efficacy of BNCT, and it was shown that there was a significant therapeutic gain. Finally, molecular targeting of the epidermal growth factor receptor (***EGFR***) has been investigated using F98 glioma cells, which had been transfected with the gene encoding ***EGFR*** and, intratumoral injection of boronated EGF as the delivery agent, followed by BNCT. These studies demonstrated that there was specific targeting of ***EGFR*** and provided proof of principle for the use of high molecular weight, receptor targeting-boron delivery agents. Finally, a xenograft model for melanoma metastatic to the brain has been developed using a human melanoma (MRA27), stereotactically implanted into the brains of nude rats, and these studies demonstrated that BNCT either cured or significantly prolonged the survival of tumor-bearing rats. It remains to be determined, which, if any, of these experimental approaches will be translated into clinical studies. Be that as it may, rat brain tumor models already have made a significant contribution to the design of clinical BNCT protocols, and should continue to do so in the future.

L4 ANSWER 19 OF 48 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 13
ACCESSION NUMBER: 2003339634 EMBASE
TITLE: Involvement of growth factor receptors of the epidermal growth factor receptor family in prostate cancer development and progression to androgen independence.
AUTHOR: Di Lorenzo G.; Bianco R.; Tortora G.; Ciardiello F.
CORPORATE SOURCE: Dr. F. Ciardiello, Cattedra di Oncologia Medica, Dipto. Med.-Chir. di Internistica, Clin. Sperim. F. Magrassi/A. Lanzara, Via S. Pansini 5, 80131 Naples, Italy. fortunatociardiello@yahoo.com
SOURCE: Clinical Prostate Cancer, (2003) 2/1 (50-57).
Refs: 97
ISSN: 1540-0352 CODEN: CPCLC4
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology

037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The development of prostate cancer and the progression from a normal prostate epithelium to androgen-dependent cancer and eventually to hormone- ***refractory*** prostate cancer is a multistep process involving several changes in the function of different growth- regulatory signals. In the past 10 years, conflicting results on epidermal growth factor receptor (***EGFR***) family expression in prostate cancer have been reported. These differences may result from technical differences, lack of standardization of immunohistochemical assays, or different scoring methodologies. Recently, 4 studies have shown experimental evidence of a role of the ***EGFR*** family, particularly ErbB-2, in the development of prostate cancer and, more specifically, in the progression to hormone- ***refractory*** clinical behavior. These 4 studies were similar in some relevant aspects, such as the patient population. In fact, the patients in each study were divided into 3 groups that represent the progression of prostate cancer. In 3 of 4 studies, a statistically significant increase in ErbB-2 expression was detected by immunohistochemistry in the progression from hormone-dependent to hormone-independent disease. The expression of ***EGFR*** was also evaluated in 1 of the 4 studies. In a recent report from our group, a significant increase in ***EGFR*** expression was observed in patients treated with radical surgery, in patients who received hormonal therapy as primary therapy before radical prostatectomy, and, finally, in patients with metastatic and hormone- ***refractory*** disease. It has been proposed that ***EGFR*** family receptors and androgen receptors function synergistically in the absence of androgen suggesting cross-talk between the ErbB-2 and androgen receptor pathways, and that mitogen -activated protein kinase and phosphatidylinositol 3-kinase can be considered the transduction pathways. Finally, clinical trials are currently in progress in patients with prostate cancer testing novel agents that selectively interfere with these receptors, such as trastuzumab, an anti-ErbB-2 monoclonal antibody, and gefitinib (ZD1839, Iressa.RTM.), a small-molecule selective ***EGFR*** tyrosine kinase inhibitor.

L4 ANSWER 20 OF 48 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2003060606 MEDLINE
DOCUMENT NUMBER: 22458555 PubMed ID: 12570681
TITLE: DAB389EGF fusion protein therapy of ***refractory*** glioblastoma multiforme.
AUTHOR: Cohen Kimberley A; Liu TieFu; Bissonette Reid; Puri Raj K; Frankel Arthur E
CORPORATE SOURCE: Department of Medicine and Comparative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.
SOURCE: Curr Pharm Biotechnol, (2003 Feb) 4 (1) 39-49. Ref: 28
Journal code: 100960530. ISSN: 1389-2010.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030207
Last Updated on STN: 20030808
Entered Medline: 20030807
AB Primary brain tumors including anaplastic astrocytomas and glioblastoma multiforme are difficult to treat because of their locally invasive nature and chemoradioresistance. Novel therapies are needed. One class of therapeutics is fusion proteins consisting of peptide toxins fused to brain tumor selective ligands. DAB389EGF is a fusion protein composed of the catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor (EGF). DAB389EGF is selectively toxic to EGF receptor (***EGFR***) overexpressing cells.

Close to half of all high-grade primary brain tumors have ***EGFR*** gene amplification and ***EGFR*** overexpression. With the use of convection-enhanced delivery (CED), DAB389EGF may be delivered locally at high concentrations to the brain tumor. CED would avoid many of the pharmacologic and toxicologic barriers which have limited effective use of this agent including rapid clearance from the circulation, high anti-diphtheria toxin antibody titers in the blood and toxicities to the liver and kidney. Both cell lines and animal models are available to assess the potential of this agent for brain tumor therapy. Since significant amounts of clinical grade DAB389EGF are available, some careful additional preclinical efficacy work should lead to testing of this agent in patients within the next few years.

L4 ANSWER 21 OF 48 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2003473281 IN-PROCESS
DOCUMENT NUMBER: 22897356 PubMed ID: 14535532
TITLE: The biology of antihormone failure in breast cancer.
AUTHOR: Nicholson Robert I; Gee Julia M W; Knowlden Janice; McClelland Richard; Madden Tracie-Ann; Barrow Denise; Hutcheson Iain
CORPORATE SOURCE: Tenovus Centre for Cancer Research, Welsh School of Pharmacy, Cardiff University, Cardiff, UK.. nicholsonri@cardiff.ac.uk
SOURCE: BREAST CANCER RESEARCH AND TREATMENT, (2003) 80 Suppl 1 S29-34; discussion S35.
Journal code: 8111104. ISSN: 0167-6806.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031011
Last Updated on STN: 20031011
AB Many estrogen receptor-positive breast cancer patients initially respond to treatment with antihormonal agents such as tamoxifen, but remissions are often followed by acquisition of resistance and ultimately disease relapse. The development of a rationale for the effective treatment of tamoxifen-resistant breast cancer requires an understanding of the complex signal transduction mechanisms that contribute towards loss of antiestrogen response. Interactions between estrogen and growth factor signaling pathways have been identified in estrogen-responsive cells that are thought to reinforce their individual cellular effects on growth and gene responses. Increasing evidence indicates that abnormalities occurring in growth factor signaling pathways, notably the epidermal growth factor receptor (***EGFR***) signaling pathway, could dramatically influence steroid hormone action and may be critical to antihormonal-resistant breast cancer cell growth. Thus, inhibitory agents targeting growth factor receptors, or their intracellular pathway components, may prove clinically beneficial in antihormone ***refractory*** disease. One example, gefitinib ('Iressa', ZD1839), an ***EGFR*** -tyrosine kinase inhibitor, is an interesting therapeutic option that may provide benefit in the treatment of antihormonal-resistant breast cancer. Rapid progress with pharmacological and molecular therapeutic agents is now being made. Therapies that target growth factor signaling pathways may prevent development of resistance.

L4 ANSWER 22 OF 48 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2002733278 MEDLINE
DOCUMENT NUMBER: 22383620 PubMed ID: 12497201
TITLE: Differential responses of ***EGFR*** -/AGT-expressing cells to the "combi-triazene" SMA41.
AUTHOR: Matheson Stephanie L; McNamee James P; Jean-Claude Bertrand J
CORPORATE SOURCE: Cancer Drug Research Laboratory, Department of Medicine, Division of Medical Oncology, McGill University Health Center/Royal Victoria Hospital, 687 Pine Avenue West, Rm. M 7.15, Montreal, Quebec, H3A 1A1, Canada.
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2003 Jan) 51 (1)

11-20.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021227
Last Updated on STN: 20030226
Entered Medline: 20030225

AB PURPOSE: Previous studies have demonstrated enhanced potency associated with the binary [DNA/epidermal growth factor receptor (***EGFR***)] targeting properties of SMA41 (a chimeric 3-(alkyl)-1,2,3-triazene linked to a 4-anilinoquinazoline backbone) in the A431 (epidermal carcinoma of the vulva) cell line. We now report on the dependence of its antiproliferative effects (e.g. DNA damage, cell survival) on the ***EGFR*** and the DNA repair protein O6-alkylguanine DNA alkyltransferase (AGT) contents of 12 solid tumor cell lines, two of which, NIH3T3 and NIH3T3 HER14 (engineered to overexpress ***EGFR***), were isogenic. METHODS: Receptor type specificity was determined using ELISA for competitive binding, as well as growth factor-stimulation assays. DNA damage was studied using single-cell microelectrophoresis (comet) assays, and levels of ***EGFR*** were determined by Western blotting. The effects of SMA41 on the cell cycle of NIH3T3 cells were investigated using univariate flow cytometry. RESULTS: Studies of receptor type specificity showed that SMA41: (a) preferentially inhibited the kinase activity of ***EGFR*** over those of Src, insulin receptor and protein kinase C (PKC, a serine/threonine kinase), (b) induced stronger inhibition of growth stimulated with EGF than of growth stimulated with platelet-derived growth factor (PDGF) or fetal bovine serum (FBS). Despite the ***EGFR*** specificity of SMA41, there was an absence of a linear correlation between the ***EGFR*** status of our solid tumor cell lines and levels of DNA damage induced by the alkylating component. Similarly, ***EGFR*** levels did not correlate with IC(50) values. The antiproliferative activities of SMA41 correlated more with the AGT status of these cells and paralleled those of the clinical triazene temozolomide (TEM). However, throughout the panel, tumor cell sensitivity to SMA41 was consistently stronger than to its closest analogue TEM. Experiments performed with the isogenic cells showed that SMA41 was capable of inducing twofold higher levels of DNA damage in the ***EGFR*** transfectant and delayed cell entry to G(2)/M in both cell types. When the cells were starved and growth-stimulated with FBS (conditions under which both cell types were growth-stimulated), in contrast to TEM, SMA41 and its hydrolytic metabolite SMA52 exhibited approximately nine- and threefold stronger inhibition of growth of the ***EGFR*** transfectant. CONCLUSIONS: These results suggest that, in addition to its ability to induce DNA damage and cell cycle perturbations, SMA41 is capable of selectively targeting the cells with a growth advantage conferred by ***EGFR*** transfection. When compared with the monoalkyltriazene prodrug TEM, its potency may be further enhanced by its ability to hydrolyze to another signal transduction inhibitor (SMA52) plus a DNA alkylating agent that may further contribute to chemosensitivity. Thus, our new "combi-targeting" strategy may well represent a tandem approach to selectively blocking receptor tyrosine kinase-mediated growth signaling while inducing significant levels of cytotoxic DNA lesions in ***refractory*** tumors.

L4 ANSWER 23 OF 48 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 2002690601 MEDLINE
DOCUMENT NUMBER: 22316667 PubMed ID: 12429632
TITLE: Expression of epidermal growth factor receptor correlates with disease relapse and progression to androgen-independence in human prostate cancer.
AUTHOR: Di Lorenzo Giuseppe; Tortora Giampaolo; D'Armiento Francesco P; De Rosa Gaetano; Staibano Stefania; Autorino Riccardo; D'Armiento Massimo; De Laurentiis Michele; De Placido Sabino; Catalano Giuseppe; Bianco A Raffaele;

Ciardiello Fortunato
CORPORATE SOURCE: Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita degli Studi di Napoli Federico II, 80131 Naples, Italy.
SOURCE: CLINICAL CANCER RESEARCH, (2002 Nov) 8 (11) 3438-44. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030617
Entered Medline: 20030616

AB PURPOSE: The transforming growth factor alpha-epidermal growth factor receptor (***EGFR***) autocrine pathway has been implicated in prostate cancer cell growth. Amplification and/or overexpression of c-erbB-2, a receptor closely related to the ***EGFR*** , has been recently involved in prostate cancer progression. We investigated ***EGFR*** and c-erbB-2 expression in primary androgen-dependent and in advanced androgen-independent prostate cancer and their potential role as markers of disease progression. EXPERIMENTAL DESIGN: ***EGFR*** and c-erbB-2 expression were evaluated by immunohistochemistry in a consecutive series of 74 prostate cancer patients with the following characteristics: 29 patients (group 1) treated with radical prostatectomy; 29 patients (group 2) treated with luteinizing hormone-releasing hormone analogues and antiandrogen therapy followed by radical prostatectomy; and 16 patients with hormone- ***refractory*** metastatic disease. In all patients we evaluated: association between ***EGFR*** and/or c-erbB-2 expression and clinicopathological parameters; and disease-free survival according to ***EGFR*** and c-erbB-2 expression in univariate analysis (Kaplan-Meier product-limit method) and in multivariate analysis (Cox proportional hazards regression model). RESULTS: ***EGFR*** expression was found in 12 of 29 (41.4%) group 1 patients, in 22 of 29 (75.9%) group 2 patients ($P < 0.0005$), and in 16 of 16 (100%) metastatic patients ($P < 0.005$), whereas c-erbB-2 expression was found in 11 of 29 (37.9%) group 1, in 10 of 29 (34.5%) group 2 patients, and in 9 of 16 (56.3%) metastatic patients. A significant association was found between ***EGFR*** expression and a high Gleason score ($P < 0.01$) and between ***EGFR*** expression and higher serum prostate-specific antigen values ($P < 0.02$) in all groups of patients. Among the 58 patients treated with radical prostatectomy, 23 of 34 ***EGFR*** -positive patients (67.6%) relapsed, whereas only 2 of 24 ***EGFR*** -negative patients (8.3%) relapsed ($P < 0.00004$). c-erbB-2 expression did not significantly correlate with disease relapse ($P = 0.07$). In a Cox multivariate analysis, the only parameter with an independent prognostic effect on disease-free survival was ***EGFR*** expression (relative hazard, 11.23; $P = 0.0014$). CONCLUSIONS: ***EGFR*** expression increases during the natural history of prostate cancer. Correlation with disease progression and hormone- ***refractory*** disease suggests that ***EGFR*** -targeted drugs could be of therapeutic relevance in prostate cancer.

L4 ANSWER 24 OF 48 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2002266675 MEDLINE
DOCUMENT NUMBER: 22000989 PubMed ID: 12006511
TITLE: Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts.
AUTHOR: Prewett Marie C; Hooper Andrea T; Bassi Rajiv; Ellis Lee M; Waksal Harlan W; Hicklin Daniel J
CORPORATE SOURCE: Department of Immunology, ImClone Systems, Inc., New York, New York 10014, USA.
SOURCE: CLINICAL CANCER RESEARCH, (2002 May) 8 (5) 994-1003. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020514
Last Updated on STN: 20021018
Entered Medline: 20021017

AB Colon carcinomas frequently express the epidermal growth factor receptor (***EGFR***), and this expression correlates with more aggressive disease and poor prognosis. Previous studies have shown that ***EGFR*** blockade by monoclonal antibody IMC-C225 can inhibit the growth of human colon carcinoma tumor cells in vitro and xenografts of these tumors in athymic mice. In this report, we have studied the in vivo activity of IMC-C225 combined with the topoisomerase I inhibitor irinotecan (CPT-11) using two models of human colorectal carcinoma in nude mice. IMC-C225 was tested at a dose of 1 or 0.5 mg administered q3d. CPT-11 was administered at a dose of 100 mg/kg/week or a maximum tolerated dose of 150 mg/kg/week. Treatment with the combination of IMC-C225 (1 and 0.5 mg) and CPT-11 (100 mg/kg) significantly inhibited the growth of established DLD-1 and HT-29 tumors compared with either CPT-11 or IMC-C225 monotherapy ($P < 0.05$). Combination therapy with IMC-C225 (1 mg) and the MTD of CPT-11 (150 mg/kg) resulted in a regression rate of 100 and 60% of established DLD-1 and HT-29 tumors, respectively. In a ***refractory*** tumor model, combined treatment with IMC-C225 and CPT-11 significantly inhibited the growth of CPT-11 ***refractory*** DLD-1 and HT-29 tumors, whereas either agent alone did not control tumor growth. Histological examination of treated tumors showed extensive tumor necrosis, decreased tumor cell proliferation, increased tumor cell apoptosis, and a marked decrease in tumor vasculature. These results suggest that ***EGFR*** blockade by IMC-C225 combined with topoisomerase I inhibitors may be an effective therapy against chemorefractory colorectal carcinoma tumors.

L4 ANSWER 25 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2002303616 MEDLINE
DOCUMENT NUMBER: 22040081 PubMed ID: 12044241
TITLE: Targeting epidermal growth factor receptor in lung cancer.
AUTHOR: Baselga Jose; Albanell Joan
CORPORATE SOURCE: Medical Oncology Service, Hospital General Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain.. baselga@hg.vhebron.es
SOURCE: Curr Oncol Rep, (2002 Jul) 4 (4) 317-24. Ref: 45
Journal code: 100888967. ISSN: 1523-3790.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020605
Last Updated on STN: 20020904
Entered Medline: 20020903

AB Among the most promising agents in clinical development to treat non-small-cell lung cancer (NSCLC) are the epidermal growth factor receptor (***EGFR***) targeting agents. A series of recent studies have demonstrated the activity of anti- ***EGFR*** targeted therapies for NSCLC. In advanced NSCLC that is ***refractory*** to chemotherapy, antitumor responses have been reported with ***EGFR*** tyrosine kinase inhibitors (ZD1839 and OSI-774). The role of ZD1839 and OSI-774 as possible additions to standard chemotherapy in the first-line setting has also been evaluated, and the studies conducted to date should respond to the question of whether these compounds could provide a survival benefit. Other areas of research involve looking at the role of ***EGFR*** tyrosine kinase inhibitors in the neoadjuvant treatment of stage III NSCLC and the planning of chemoprevention studies. These exciting results and plans are further complemented by an emerging number of compounds in clinical development, including both monoclonal antibodies

(ie, IMC-C225) and other tyrosine kinase inhibitors, directed at the ***EGFR*** .

L4 ANSWER 26 OF 48 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 2002378205 MEDLINE
DOCUMENT NUMBER: 22119380 PubMed ID: 12124830
TITLE: Absence of c-KIT and members of the epidermal growth factor receptor family in ***refractory*** germ cell cancer.
COMMENT: Comment in: Cancer. 2003 Jun 1;97(11):2926-7; author reply 2927-8
AUTHOR: Kollmannsberger C; Mayer F; Pressler H; Koch S; Kanz L; Oosterhuis J W; Looijenga L H J; Bokemeyer C
CORPORATE SOURCE: Department of Internal Medicine, University of Tuebingen Medical Center, Tuebingen, Germany.
SOURCE: CANCER, (2002 Jul 15) 95 (2) 301-8.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020719
Last Updated on STN: 20020809
Entered Medline: 20020808
AB BACKGROUND: Germ cell tumors (GCTs) in adolescent and young males are very sensitive to cisplatin-based chemotherapy. However, 10-20% of the patients cannot be cured by currently available therapeutic options. Once a tumor does not respond to cisplatin, current therapeutic modalities offer only a chance for short palliation. Recently, new treatment options that interfere with various receptor tyrosine kinases, including c-KIT and members of the epidermal growth factor receptor (***EGFR***) family, have been used successfully in chemotherapy-resistant tumors overexpressing c-KIT, ERB-B2, or ***EGFR*** . METHODS: We studied the presence of c-KIT and the four members of the ***EGFR*** family by immunohistochemistry, as well as by ERB-B2 gene amplification using fluorescent in situ hybridization, in a series of 22 patients with cisplatin-resistant GCTs in search of new treatment targets. The results in these ***refractory*** tumors were compared with those of 12 patients with chemosensitive GCTs diagnosed in an advanced metastatic stage. RESULTS: The data obtained in both groups did not differ in any of the investigated biologic markers. c-KIT was detected in the one case of pure seminoma studied and in the seminomatous components of combined tumors. The presence of ***EGFR*** was restricted to trophoblastic giant cells and the syncytiotrophoblastic elements of four nonseminomas including one pure choriocarcinoma and to a secondary non-germ cell malignancy, which had developed most likely from a mature teratoma. ERB-B2 was moderately positive in the secondary non-germ cell malignancy, in one mature teratoma component of a mixed nonseminoma, and together with ***EGFR*** in the syncytiotrophoblastic cells of a pure choriocarcinoma. Of all samples investigated, this latter case was the only one showing an amplification of the ERB-B2 gene in the syncytiotrophoblasts. ERB-B3 and ERB-B4 were detected rarely. CONCLUSION: The majority of ***refractory*** GCTs do not qualify for treatment with new biologic agents targeting the receptor tyrosine kinases ***EGFR*** , ERB-B2, or c-KIT. The lack of differences between the tumors of ***refractory*** and the responsive patients indicates that overexpression of any of these receptor tyrosine kinases does not contribute to a resistant phenotype in GCTs.
DOI 10.1002/cncr.10671

L4 ANSWER 27 OF 48 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 2002065869 MEDLINE
DOCUMENT NUMBER: 21650954 PubMed ID: 11791182
TITLE: Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family.
AUTHOR: Bishop Philippe C; Myers Timothy; Robey Robert; Fry David W; Liu Edison T; Blagosklonny Mikhail V; Bates Susan E

CORPORATE SOURCE: Medicine Branch, NCI, NIH, Bethesda, Maryland, MD 20892, USA, and FDA/CBER/OTRR/DCTDA/Oncology Branch, HFM-573, Rockville, Maryland, MD 20852, USA.
SOURCE: ONCOGENE, (2002 Jan 3) 21 (1) 119-27.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020220
Entered Medline: 20020219

AB Clinical responses to the ***HER1*** (EGF receptor) inhibitors and HER2/neu/ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be ***refractory*** to treatment. We have observed similar results in the 60 cell lines of the NCI Anti-Cancer Drug Screen using a panel of 11 selective ***HER1*** inhibitors. As expected, low ***HER1*** -expressing cell lines were insensitive to ***HER1*** inhibitors. In cell lines with high ***HER1*** expression, low concentrations of ***HER1*** inhibitors potently inhibit both ***HER1*** phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High ***HER1*** -expressing cell lines can be subdivided into two groups based on their sensitivity to ***HER1*** inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at sub-micromolar concentrations of ***HER1*** inhibitors. In the insensitive group, receptor inhibition occurred at a low concentration (< 1 microM) but concentrations that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only drug-sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to ***HER1*** inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of ***HER1*** inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to ***HER1*** inhibitors in a large subset of cancer cell lines.

L4 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:871186 CAPLUS
DOCUMENT NUMBER: 137:368064
TITLE: Safety experience with IMC-C225, an anti-epidermal growth factor receptor antibody
AUTHOR(S): Needle, Michael N.
CORPORATE SOURCE: Department of Clinical Affairs, ImClone Systems Incorporated, Somerville, NJ, USA
SOURCE: Seminars in Oncology (2002), 29(5, Suppl. 14), 55-60
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. In phase II trials, the anti-epidermal growth factor receptor antibody IMC-C225 did not appear to significantly exacerbate the common toxicities assocd. with cytotoxic chemotherapy when combined with std. anticancer treatments in patients with colorectal cancer, squamous cell carcinoma of the head and neck, or pancreatic cancer. The most common treatment-related adverse events reported during therapy with IMC-C225 were an acne-like rash and hypersensitivity reactions. The acne-like rash appeared as a sterile, suppurative form of folliculitis, commonly starting on the face, scalp, chest, and upper back. It resolved without scarring once treatment was stopped. Notably, the appearance of acne-like rash, particularly grade 3, was assocd. with higher treatment responses in patients with ***refractory*** colorectal cancer. The hypersensitivity reactions occurred less often than acne-like rash. They

responded to std. treatments and were less common after the first dose. In summary, IMC-C225 is generally well tolerated as a single agent and when combined with chemotherapy or radiotherapy and possesses a manageable toxicity profile.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 48 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 2002718785 MEDLINE
DOCUMENT NUMBER: 22368897 PubMed ID: 12480194
TITLE: Molecular markers and targeted therapy with novel agents: prospects in the treatment of non-small cell lung cancer.
AUTHOR: Rosell Rafael; Fossella Frank; Milas Luka
CORPORATE SOURCE: Hospital Germans Trias i Pujol, Medical Oncology Service, Ctra Canyet, s/n 08916 Badalona, Barcelona, Spain. (Spanish Lung Cancer Group). rrosell@ns.hugtip.scs.es
SOURCE: LUNG CANCER, (2002 Dec) 38 Suppl 4 43-9. Ref: 48
Journal code: 8800805. ISSN: 0169-5002.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20021218
Last Updated on STN: 20030619
Entered Medline: 20030618

AB Detection of genomic differences predictive of drug response or resistance in individual patients may allow therapy to be customized to the characteristics of particular tumors. Preliminary findings are that non-small cell lung cancer patients overexpressing ERCC1 mRNA have lower response to cisplatin chemotherapy, while those overexpressing ribonucleotide reductase mRNA have limited benefit from gemcitabine. In addition, overexpression of beta-tubulin III and stathmin can influence the sensitivity to microtubule interacting drugs, like vinorelbine and paclitaxel. The introduction of biological agents which target highly specific intracellular pathways offers the promise of enhancing the efficacy of cytotoxic chemotherapy. Among many promising biological agents is the monoclonal antibody C225, which blocks the ***EGFR*** receptor. The addition of C225 appears to induce responses in a proportion of colon cancer patients ***refractory*** to 5-FU or irinotecan, supporting pre-clinical evidence of synergistic activity. It also appears from xenograft data that C225 enhances the sensitivity of tumors to radiation and docetaxel or the combination.

L4 ANSWER 30 OF 48 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 2002662341 MEDLINE
DOCUMENT NUMBER: 22309711 PubMed ID: 12422312
TITLE: Epidermal growth factor receptor expression, signal pathway, and inhibitors in non-small cell lung cancer.
AUTHOR: Bunn Paul A Jr; Franklin Wilbur
CORPORATE SOURCE: Departments of Medicine and Pathology, the University of Colorado Health Sciences Center, Denver, CO 80262, USA.
CONTRACT NUMBER: CA 46934 (NCI)
CA 58187 (NCI)
SOURCE: SEMINARS IN ONCOLOGY, (2002 Oct) 29 (5 Suppl 14) 38-44.
Ref: 51
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211

ENTRY DATE: Entered STN: 20021108
Last Updated on STN: 20021212
Entered Medline: 20021114

AB The majority of non-small cell lung cancers (NSCLCs) overexpress the epidermal growth factor receptor (***EGFR***). The ***EGFR*** is frequently overexpressed in preneoplastic bronchial lesions. Thus, ***EGFR*** is an excellent potential target for prevention and therapy. New agents developed to inhibit ***EGFR*** function include monoclonal antibodies to ***EGFR*** and small-molecule receptor tyrosine kinase inhibitors. Preclinical studies showed that both types of inhibitors blocked the in vitro growth of human NSCLC cell lines by inhibiting receptor phosphorylation and phosphorylation of downstream proteins including MAP kinases and AKT. Both types of inhibitors also slowed the growth of human NSCLC tumors in nude mice. Additive or synergistic growth inhibition resulted from the combination of either type of inhibitor with chemotherapy and/or radiotherapy. Clinical phase I and phase II trials showed that both types of inhibitors could be delivered safely, and serum concentrations equivalent to or higher than those required for in vitro activity were achieved. Skin rash was the dose-limiting toxicity with all inhibitors. The skin rash was dose related and reversible. Objective responses were observed in advanced-stage patients ***refractory*** to chemotherapy, though the responses were partial responses. Response rates appear higher when the inhibitors are combined with chemotherapy. The results of randomized trials comparing the use of chemotherapy alone with chemotherapy plus the inhibitors are eagerly awaited.

L4 ANSWER 31 OF 48 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 2002662339 MEDLINE
DOCUMENT NUMBER: 22309709 PubMed ID: 12422310
TITLE: IMC-C225, an anti-epidermal growth factor receptor monoclonal antibody for treatment of head and neck cancer.
AUTHOR: Herbst Roy S; Hong Waun Ki
CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.
SOURCE: SEMINARS IN ONCOLOGY, (2002 Oct) 29 (5 Suppl 14) 18-30.
Ref: 96
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021108
Last Updated on STN: 20021212
Entered Medline: 20021114

AB Squamous cell carcinoma of the head and neck remains a clinical challenge because of the high rate of locoregional disease recurrence. The importance of the epidermal growth factor receptor (***EGFR***) in the development and progression of many solid tumors, including squamous cell carcinoma of the head and neck, is well understood; increased expression is associated with enhanced tumor invasiveness, resistance to chemotherapy, and a lower patient survival rate. Several approaches have been developed to achieve ***EGFR*** blockade as an anticancer treatment strategy, including the anti- ***EGFR*** monoclonal antibody IMC-C225, which competitively binds to the extracellular receptor site and prevents binding by the natural ***EGFR*** ligands EGF and transforming growth factor-alpha. Preclinical studies to evaluate IMC-225 in human cancer cell lines in vitro and human tumor xenografts in vivo have shown its potent antitumor activity. Clinical efficacy of IMC-C225 appears to involve multiple mechanisms, including inhibition of cell cycle progression, induction of apoptosis, inhibition of angiogenesis, inhibition of metastasis, and enhancement of the response to chemotherapy and radiation therapy. Phase I studies of IMC-C225 combined with

chemotherapy or radiation showed promising response rates in patients with recurrent or ***refractory*** squamous cell carcinoma of the head and neck. Phase II and III trials to examine the efficacy and safety of these combinations are currently underway. To date, IMC-C225 has been well tolerated, with skin rashes and allergic reactions being the most clinically important adverse events reported. IMC-C225 displays dose-dependent elimination characteristics and a half-life of approximately 7 days. Current recommendations for dosing include a 400 mg/m(2) loading dose, followed by weekly infusions at 250 mg/m(2).

L4 ANSWER 32 OF 48 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 2001374563 MEDLINE
DOCUMENT NUMBER: 21324330 PubMed ID: 11431346
TITLE: Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis.
AUTHOR: Viloria-Petit A; Crombet T; Jothy S; Hicklin D; Bohlen P; Schlaeppi J M; Rak J; Kerbel R S
CORPORATE SOURCE: Molecular and Cellular Biology Research, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario M4N 3M5, Canada.
CONTRACT NUMBER: CA-41233 (NCI)
SOURCE: CANCER RESEARCH, (2001 Jul 1) 61 (13) 5090-101. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Inhibitors of epidermal growth factor receptor (***EGFR***) signaling are among the novel drugs showing great promise for cancer treatment in the clinic. However, the possibility of acquired resistance to such drugs because of tumor cell genetic instabilities has not yet been explored. Here we report the experimental derivation and properties of such cell variants obtained from recurrent tumor xenografts of the human A431 squamous cell carcinoma, after two consecutive cycles of therapy with one of three different anti- ***EGFR*** monoclonal antibodies: mR3, hR3, or C225. Initial response to a 2-week period of treatment was generally total tumor regression and was not significantly different among the three antibody groups. However, tumors often reappeared at the site of inoculation, generally after prolonged latency periods, and most of the tumors became ***refractory*** to a second round of therapy. Cell lines established from such resistant tumors retained high ***EGFR*** expression, normal sensitivity to anti- ***EGFR*** antibody or ligand, and unaltered growth rate when compared with the parental line in vitro. In contrast, the A431 cell variants exhibited an accelerated growth rate and a significantly attenuated response to anti- ***EGFR*** antibodies in vivo relative to the parental line. Because of the reported suppressive effect of ***EGFR*** inhibitors on vascular endothelial growth factor (VEGF) expression, and the demonstrated role of VEGF in the angiogenesis and growth of A431 tumor xenografts, relative VEGF expression was examined. Five of six resistant variants expressed increased levels of VEGF, which paralleled an increase in both angiogenic potential in vitro and tumor angiogenesis in vivo. In addition, elevated expression of VEGF in variants of A431 cells obtained by gene transfection rendered the cells significantly resistant to anti- ***EGFR*** antibodies in vivo. Taken together, the results suggest that, at least in the A431 system, variants displaying acquired resistance to anti- ***EGFR*** antibodies can emerge in vivo and can do so, at least in part, by mechanisms involving the selection of tumor cell subpopulations with increased angiogenic potential.

L4 ANSWER 33 OF 48 MEDLINE on STN DUPLICATE 25

ACCESSION NUMBER: 2001681577 MEDLINE
DOCUMENT NUMBER: 21584872 PubMed ID: 11727507
TITLE: IMC-C225, an anti-epidermal growth factor receptor monoclonal antibody, for treatment of head and neck cancer.
AUTHOR: Herbst R S; Kim E S; Harari P M
CORPORATE SOURCE: Department of Thoracic & Head and Neck Medical Oncology, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.. rherbst@mdanderson.org
SOURCE: Expert Opin Biol Ther, (2001 Jul) 1 (4) 719-32. Ref: 100
Journal code: 101125414. ISSN: 1471-2598.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020207
Entered Medline: 20020206

AB Squamous cell carcinoma (SCC) of the head and neck (H&N) remains a clinical challenge due to its high rate of locoregional disease recurrence. The importance of the epidermal growth factor receptor (***EGFR***) in the development and progression of many solid tumours (including SCC of the H&N) is well understood; increased expression is associated with enhanced tumour invasion, resistance to chemotherapy and decreased patient survival. Several approaches have been developed to achieve ***EGFR*** blockade as an anticancer treatment strategy, including an anti- ***EGFR*** monoclonal antibody (mAb), IMC-C225, which competitively binds to the extracellular receptor site to prevent binding by natural ***EGFR*** ligands (EGF and TGF-alpha). Preclinical studies evaluating this chimeric mAb in human cancer cell lines in vitro and human tumour xenografts in vivo have demonstrated its potent antitumour activity. The clinical efficacy of IMC-C225 appears to involve multiple anticancer mechanisms, including inhibition of cell cycle progression, induction of apoptosis, anti-angiogenesis, inhibition of metastasis and its ability to enhance the response to chemotherapy and radiation therapy. Phase I studies of IMC-C225 combined with chemotherapy or radiation for SCC of the H&N demonstrate excellent response rates in patients with recurrent or ***refractory*** disease. Phase II and III trials examining the efficacy and safety of these combinations are currently underway. To date, IMC-C225 has been well-tolerated, with skin rashes and allergic reactions being the most clinically important adverse events reported. IMC-C225 displays dose-dependent elimination characteristics and a half-life of approximately 7 days. Current recommendations for dosing include a 400 mg/m2 loading dose, followed by weekly infusions of 250 mg/m2.

L4 ANSWER 34 OF 48 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 2001248971 MEDLINE
DOCUMENT NUMBER: 21201365 PubMed ID: 11304572
TITLE: Accumulation of allelic changes at chromosomes 7p, 18q, and 2 in parathyroid lesions of uremic patients.
AUTHOR: Nagy A; Chudek J; Kovacs G
CORPORATE SOURCE: Laboratory of Molecular Oncology, Department of Urology, Ruprecht-Karls University, Heidelberg, Germany.
SOURCE: LABORATORY INVESTIGATION, (2001 Apr) 81 (4) 527-33.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

AB We examined by microsatellite allelotyping 69 hyperplastic lesions of the

parathyroid glands from 23 patients with ***refractory*** , uremic hyperparathyroidism. Allelic changes, at least at one chromosomal arm, were found in 31 of the 69 lesions (43%). Alteration at a single chromosome was seen in 14 lesions and at two to four chromosomes in 11 lesions, and there were five to eight alterations in 5 nodules. Allelic imbalance occurred most frequently at chromosome 7p between the ***EGFR*** gene and locus D7S817 (16%), at 18q between loci D18S61 and D18S70 (14%), and at chromosome 2 between D2S380 and D2S1391 (9%). X-inactivation study showed a monoclonal growth in 18 of 29 nodules in females, and a loss of the Y chromosome was seen in 8 of the 39 nodules obtained from males. Our results suggest that the uremic "hyperplastic" nodules have a molecular pathway distinct from those known for sporadic primary parathyroid adenomas.

L4 ANSWER 35 OF 48 MEDLINE on STN DUPLICATE 27
ACCESSION NUMBER: 2001154026 MEDLINE
DOCUMENT NUMBER: 21102057 PubMed ID: 11169460
TITLE: Regulation of heparin-binding EGF-like growth factor expression in Ha-ras transformed human mammary epithelial cells.
AUTHOR: Martinez-Lacaci I; De Santis M; Kannan S; Bianco C; Kim N; Wallace-Jones B; Wechselberger C; Ebert A D; Salomon D S
CORPORATE SOURCE: Tumor Growth Factor Section, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (2001 Feb) 186 (2) 233-42. Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322
AB Heparin-binding epidermal growth factor-like growth factor (HB-EGF) mRNA and protein expression is induced by EGF in MCF-10A nontransformed and Ha-ras transfected human mammary epithelial cells. The anti-EGF receptor (***EGFR***) blocking monoclonal antibody (MAb) 225 and the ***EGFR*** tyrosine kinase inhibitor PD153035 were able to inhibit the induction of HB-EGF mRNA levels in MCF-10A cells. However, the Ha-ras transformed MCF-10A cells were more ***refractory*** to inhibition by these agents and only a combination of the 225 MAb and PD153035 was able to significantly abrogate HB-EGF induction by EGF. The anti-erbB2 MAb L26 which interferes with heterodimer formation was able to block HB-EGF induction in response to EGF in MCF-10A cells and in the Ha-ras transformed cells only when used in combination with either the 225 MAb or PD153035. The MEK inhibitor PD90859 completely blocked EGF induction of HB-EGF mRNA levels in the nontransformed and Ha-ras transformed MCF-10A cells, which indicates that MAPK is involved in the signaling pathway of HB-EGF induction by EGF. An increase in the levels of HB-EGF may, therefore, be an important contributor to oncogenic transformation that is caused by Ha-ras overexpression in mammary epithelial cells. J. Cell. Physiol. 186:233-242, 2001. Published 2001 Wiley-Liss, Inc.

L4 ANSWER 36 OF 48 MEDLINE on STN DUPLICATE 28
ACCESSION NUMBER: 2000354719 MEDLINE
DOCUMENT NUMBER: 20354719 PubMed ID: 10898354
TITLE: Developments in chemotherapy of breast cancer.
AUTHOR: Hortobagyi G N
CORPORATE SOURCE: Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston 77030-4009, USA.
SOURCE: CANCER, (2000 Jun 15) 88 (12 Suppl) 3073-9. Ref: 96
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000727

AB BACKGROUND: Breast carcinoma is moderately sensitive to multiple antitumor agents. Cytotoxic combination regimens developed in the 1970s were shown to produce higher response rates and longer durations of response and survival than single-agent therapy. These regimens became the standard of care for the management of metastatic, hormone- ***refractory*** breast carcinoma, and more recently, for primary breast carcinoma. Randomized trials also have demonstrated that anthracycline-containing combinations were more effective than combinations without anthracyclines. The development of several new cytotoxic agents and novel antitumor strategies prompted this review. METHODS: The author conducted a computerized literature search of MEDLINE and CANCERLIT and also reviewed the abstracts of major oncology meetings (ASCO, American Association for Cancer Research, ESMO, and San Antonio Breast Cancer Symposium) over the past 10 years. RESULTS: Effective new cytotoxic drugs include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and capecitabine. The identification of specific molecular abnormalities (HER-2/neu or epidermal growth factor receptor [***EGFR***] overexpression) led to the development of targeted therapeutic intervention (monoclonal antibodies and tyrosine kinase inhibitors). Trastuzumab, a monoclonal antibody against the HER-2/neu oncoprotein, produced objective regression in 15-20% of patients with HER-2/neu-overexpressing breast carcinoma and improved the efficacy of paclitaxel. Other productive directions of therapeutic research include inhibition of intracellular signaling, interference with tumor angiogenesis, cell cycle regulation, and the development of vaccines. CONCLUSIONS: Expanded understanding of the biology of breast carcinoma led to the development of rational therapeutic interventions, many of which are currently under active clinical development.

L4 ANSWER 37 OF 48 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 2000309924 MEDLINE
DOCUMENT NUMBER: 20309924 PubMed ID: 10851066
TITLE: Interaction between protein tyrosine phosphatase and protein tyrosine kinase is involved in androgen-promoted growth of human prostate cancer cells.
AUTHOR: Meng T C; Lee M S; Lin M F
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, NE 68198, USA.
CONTRACT NUMBER: CA72274 (NCI)
SOURCE: ONCOGENE, (2000 May 18) 19 (22) 2664-77.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000627

AB Steroid hormones play key roles in regulating cell proliferation and differentiation in targeting tissues. However, in advanced cancers, the steroid hormone regulation is frequently attenuated through a yet unknown mechanism even in the presence of functional steroid hormone receptors. We investigate the functional role of tyrosine phosphorylation signaling in the hormone- ***refractory*** growth of human prostate tumors. Initial studies demonstrate that the androgen-responsive phenotype of human prostate cancer cells associates with a low phosphotyrosine (p-Tyr) level of ErbB-2, which is regulated by cellular prostatic acid phosphatase (PAcP), a protein tyrosine phosphatase. In prostate cancer cells, the

p-Tyr level, but not the protein level, of ErbB-2 inversely correlates with the androgen-responsiveness of cell proliferation. Androgen-stimulated cell growth concurs with a down-regulation of cellular PAcP, an elevated p-Tyr level of ErbB-2, and the activation of mitogen-activated protein kinases. Furthermore, only the ErbB-2 inhibitor AG 879, but not the ***EGFR*** inhibitor AG 1478, abolishes androgen-induced cell proliferation. Forced expression of ErbB-2 can also attenuate androgen promotion of cell growth. Data taken collectively conclude that in human prostate cancer cells, the tyrosine phosphorylation of ErbB-2 regulated by cellular PAcP plays a key role in regulating androgen-mediated proliferation signaling. Oncogene (2000).

L4 ANSWER 38 OF 48 MEDLINE on STN DUPLICATE 30
ACCESSION NUMBER: 2000444993 MEDLINE
DOCUMENT NUMBER: 20449492 PubMed ID: 10992426
TITLE: CL1-GFP: an androgen independent metastatic tumor model for prostate cancer.
AUTHOR: Patel B J; Pantuck A J; Zisman A; Tsui K H; Paik S H; Caliliw R; Sheriff S; Wu L; deKernion J B; Tso C L; Belldegrun A S
CORPORATE SOURCE: Department of Urology, University of California at Los Angeles, Los Angeles, California 90095-1738, USA.
SOURCE: JOURNAL OF UROLOGY, (2000 Oct) 164 (4) 1420-5. Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001005
AB PURPOSE: The mechanisms responsible for tumor progression to androgen independence in prostate cancer (CaP) remain unknown. To characterize these changes and provide a basis for rational therapeutic strategies for advanced CaP, an in vivo model from a highly aggressive androgen independent CaP cell line with distinct cellular and molecular properties was developed. MATERIALS AND METHODS: An aggressive androgen-independent cell line designated CL1 was derived from a slow-growing, and androgen-dependent, parental LNCaP cell line through in-vitro androgen-deprivation and selection. CL1 was stably transfected with a green fluorescence protein gene (CL1-GFP) and orthotopically injected into SCID mice. The pathologic behavior, histology, and molecular determinants of CL1 tumor and metastases were determined and characterized by standard light and fluorescent microscopy, and quantitative RT-PCR analysis. RESULTS: CL1 is an anaplastic prostate cancer cell line which demonstrates extensive local invasion and metastases to various organs that can be visualized via GFP expression. When compared with parental LNCaP cells, RT-PCR analysis of the tumor revealed an over-expression of ***EGFR*** , b-FGF, VEGF, TGF-beta, IL-8, IL-6, and bcl-2 and a down regulated expression of the p53, E-cadherin and PTEN. In contrast to LNCaP cells, CL1 tumors express lower levels of androgen receptor and barely detectable PSA mRNA. CONCLUSIONS: CL1-GFP represents an aggressive androgen-independent CaP tumor model derived through androgen deprivation whose pathologic development and molecular properties in animals resembles the clinical characteristics of hormone ***refractory*** prostate cancer (HRPC). Metastatic sites of CL1-GFP can be visualized with fluorescence microscopy offering a unique therapeutic model for the evaluation of drug sensitivity and other therapeutic modalities.

L4 ANSWER 39 OF 48 MEDLINE on STN DUPLICATE 31
ACCESSION NUMBER: 2000268193 MEDLINE
DOCUMENT NUMBER: 20268193 PubMed ID: 10806474
TITLE: FAK integrates growth-factor and integrin signals to promote cell migration.
AUTHOR: Sieg D J; Hauck C R; Ilic D; Klingbeil C K; Schaefer E; Damsky C H; Schlaepfer D D

CORPORATE SOURCE: Department of Immunology, The Scripps Research Institute, La Jolla, CA 92037, USA.
SOURCE: NATURE CELL BIOLOGY, (2000 May) 2 (5) 249-56.
Journal code: 100890575. ISSN: 1465-7392.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000802

AB Here we show that cells lacking focal adhesion kinase (FAK) are ***refractory*** to motility signals from platelet-derived and epidermal growth factors (PDGF and EGF respectively), and that stable re-expression of FAK rescues these defects. FAK associates with activated PDGF- and EGF-receptor (PDGFR and ***EGFR***) signalling complexes, and expression of the band-4.1-like domain at the FAK amino terminus is sufficient to mediate an interaction with activated ***EGFR*** . However, efficient EGF-stimulated cell migration also requires FAK to be targeted, by its carboxy-terminal domain, to sites of integrin-receptor clustering. Although the kinase activity of FAK is not needed to promote PDGF- or EGF-stimulated cell motility, kinase-inactive FAK is transphosphorylated at the indispensable Src-kinase-binding site, FAK Y397, after EGF stimulation of cells. Our results establish that FAK is an important receptor-proximal link between growth-factor-receptor and integrin signalling pathways.

L4 ANSWER 40 OF 48 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:112494 CAPLUS
DOCUMENT NUMBER: 130:309820
TITLE: Redundancy of autocrine loops in human osteosarcoma cells
AUTHOR(S): Benini, Stefania; Baldini, Nicola; Manara, Maria Cristina; Chano, Tokuhiro; Serra, Massimo; Rizzi, Simona; Lollini, Pier-Luigi; Picci, Piero; Scotlandi, Katia
CORPORATE SOURCE: Laboratorio di Ricerca Oncologica, Istituti Ortopedici Rizzoli, Bologna, Italy
SOURCE: International Journal of Cancer (1999), 80(4), 581-588
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB With the aim of identifying innovative therapeutic strategies for osteosarcoma patients who are ***refractory*** to conventional chemotherapy, we analyzed the in vitro effects of the blockage of autocrine circuits. Since the insulin-like growth factor-I receptor (IGF-IR)-mediated loop is relevant to the growth of osteosarcoma, we analyzed the activity of the IGF-IR-blocking antibody .alpha.IR3 in both sensitive and multidrug-resistant osteosarcoma cell lines. Only limited effects, however, were obsd., suggesting the simultaneous existence of other autocrine circuits. Indeed, in a representative panel of 12 human osteosarcoma cell lines, in addn. to the IGF-IR-mediated circuit, we demonstrated also a loop mediated by epidermal growth factor receptor as well as the presence of nerve growth factor, low-affinity nerve growth factor receptor as well as tyrosine receptor kinase A in the great majority of osteosarcomas. Therapies based on the inhibition of single circuits may have only limited effects in osteosarcoma, whereas the use of suramin, a drug which, besides other activities, non-selectively interferes with the binding of growth factors to their receptors, appears as a promising alternative, in both sensitive and drug-resistant osteosarcoma cells.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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on STN
ACCESSION NUMBER: 2000175394 EMBASE
TITLE: Glioblastoma multiforme: Change in management strategies and outcome?.
AUTHOR: Morgalla M.H.; Nagele T.; Heiss E.; Grote E.H.
CORPORATE SOURCE: M.H. Morgalla, Division of Neurosurgery, University of Tuebingen, Hoppe-Seyler-Str. 3, D-72076 Tuebingen, Germany. 0707166839-0001@t-online.de
SOURCE: Neurology Psychiatry and Brain Research, (1999) 7/3 (113-120).
Refs: 53
ISSN: 0941-9500 CODEN: NPBRE4
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The overall prognosis for patients with glioblastoma multiforme (GBM) remains poor. These tumors are highly aggressive and often ***refractory*** to radiation and other adjuvant therapies in standard use today. The mean survival for most patients is still less than 24 months. Management therefore consists of tumor control without additional loss of quality of life. Surgery exhibits only one mode of the overall treatment plan. It decreases the tumor size and is therefore essential. Biopsy allows diagnosis and tumor grading. Radiation and chemotherapy are still adjuvant modes of therapy, but can extend the life span only briefly. Gene therapy is a new approach in the management of glioblastoma multiforme. The deregulated expression of one or more growth control genes including p16, p53, EGF receptor (***EGFR***), MDM2 or Bcl-2 may be responsible for the treatment resistance of the phenotype of GBM. However, there is no clinical evidence so far that gene therapy increases survival rates of patients with GBM.

L4 ANSWER 42 OF 48 MEDLINE on STN DUPLICATE 32
ACCESSION NUMBER: 1998369080 MEDLINE
DOCUMENT NUMBER: 98369080 PubMed ID: 9703473
TITLE: 2-Substituted aminopyrido[2,3-d]pyrimidin-7(8H)-ones. structure-activity relationships against selected tyrosine kinases and in vitro and in vivo anticancer activity.
AUTHOR: Klutchko S R; Hamby J M; Boschelli D H; Wu Z; Kraker A J; Amar A M; Hartl B G; Shen C; Klohs W D; Steinkampf R W; Driscoll D L; Nelson J M; Elliott W L; Roberts B J; Stoner C L; Vincent P W; Dykes D J; Panek R L; Lu G H; Major T C; Dahring T K; Hallak H; Bradford L A; Showalter H D; Doherty A M
CORPORATE SOURCE: Department of Chemistry, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105, USA.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1998 Aug 13) 41 (17) 3276-92.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 20000303
Entered Medline: 19980909
AB While engaged in therapeutic intervention against a number of proliferative diseases, we have discovered the 2-aminopyrido[2, 3-d]pyrimidin-7(8H)-ones as a novel class of potent, broadly active tyrosine kinase (TK) inhibitors. An efficient route was developed that enabled the synthesis of a wide variety of analogues with substitution on several positions of the template. From the lead structure 2, a series of analogues bearing variable substituents at the C-2 position and methyl or

ethyl at N-8 was made. Compounds of this series were competitive with ATP and displayed submicromolar to low nanomolar potency against a panel of TKs, including receptor (platelet-derived growth factor, PDGFr; fibroblast growth factor, FGFr; epidermal growth factor, ***EGFr***) and nonreceptor (c-Src) classes. One of the more thoroughly evaluated members was 63 with IC50 values of 0.079 microM (PDGFr), 0.043 microM (bFGFr), 0.044 microM (***EGFr***), and 0.009 microM (c-Src). In cellular studies, 63 inhibited PDGF-mediated receptor autophosphorylation in a number of cell lines at IC50 values of 0.026-0.002 microM and proliferation of two PDGF-dependent lines at 0.3 microM. It also caused inhibition of soft agar colony formation in three cell lines that overexpress the c-Src TK, with IC50 values of 0.33-1.8 microM. In in vivo studies against a panel of seven xenograft tumor models with known and/or inferred dependence on the ***EGFr*** , PDGFr, and c-Src TKs, compound 63 produced a tumor growth delay of 10.6 days against the relatively ***refractory*** SK-OV-3 ovarian xenograft and also displayed activity against the HT-29 tumor. In rat oral bioavailability studies, compound 63 plasma concentrations declined in a biexponential manner, and systemic plasma clearance was high relative to liver blood flow. Finally, in rat metabolism studies, HPLC chromatography identified two metabolites of 63, which were proved by mass spectrometry and synthesis to be the primary amine (58) and N-oxide (66). Because of the excellent potency of 63 against selected TKs, in vitro and in vivo studies are underway for this compound in additional tumor models dependent upon PDGFr, FGFr, and c-Src to assess its potential for advancement to clinical trials.

L4 ANSWER 43 OF 48 MEDLINE on STN DUPLICATE 33
ACCESSION NUMBER: 1998098165 MEDLINE
DOCUMENT NUMBER: 98098165 PubMed ID: 9435876
TITLE: Clinical experience with CD64-directed immunotherapy. An overview.
AUTHOR: Curnow R T
CORPORATE SOURCE: Medarex Inc., Annadale, NJ 08801, USA.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1997 Nov-Dec) 45 (3-4) 210-5. Ref: 9
Journal code: 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 20000303
Entered Medline: 19980129

AB The class I IgG receptor (Fc gamma RI or CD64 receptor), which is present on key cytotoxic effector cells, has been shown to initiate the destruction of tumor cells in vitro and has been hypothesized to play a role in the destruction of antibody-coated cells such as platelets in idiopathic thrombocytopenia purpura (ITP). This overview summarizes the clinical experience with CD64-directed immunotherapy in cancer patients with the bispecific antibodies MDX-447 [humanized Fab anti-CD64 x humanized Fab anti-(epidermal growth factor receptor, ***EGFR***)] and MDX-H210 (humanized Fab anti-DC64 x Fab anti-HER2/neu), and with the anti-CD64 monoclonal antibody (mAB) MDX-33 (H22) in the modulation of monocyte CD64 in vivo. In an ongoing phase I/II open-label trial with progressive dose escalation (1-15 mg/m2), patients with treatment ***refractory*** ***EGFR*** -positive cancers (renal cell carcinoma (RCC), head and neck, bladder, ovarian, prostate cancer and skin cancer) are treated weekly with intravenous MDX-447, with and without granulocyte-colony-stimulating factor (G-CSF). MDX-447 has been found to be immunologically active at all doses, binding to circulating monocytes and neutrophils (when given with G-CSF), causing monocytopenia and stimulating increases in circulating plasma cytokines. MDX-447 is well tolerated, the primary toxicities being fever, chills, blood pressure lability, and pain/ myalgias. Of 36 patients evaluable for response, 9

have experienced stable disease of 3-6 month's duration. The optimal dose and the maximal tolerated dose (MTD) have yet to be defined; dose escalation continues to define better the dose, toxicity, and the potential therapeutic role of this bispecific antibody. Three MDX-H210 phase II trials are currently in progress, all using the intravenous dose of 15 mg/m2 given with granulocyte/macrophage (GM-CSF). These consist of one trial each in the treatment of RCC patients, patients with prostate cancer, and colorectal cancer patients, all of whom have failed standard therapy. At the time of writing, 11 patients have been treated in these phase II trials. Four patients have demonstrated antitumor effects. Patients demonstrating responses include 2 with RCC and 2 with prostate cancer. One RCC patient has had a 54% reduction in size of a hepatic metastatic lesion and the other has had a 49% decrease in the size of a lung metastasis with simultaneous clearing of other non-measurable lung lesions. Regarding the two patients with prostate cancer, one has had a 90% reduction in serum prostate-specific antigen (PSA; 118-11 ng/ml), which has persisted for several months; the other patient with prostate has had a 70% reduction of serum PSA (872 ng/ml to 208 ng/ml) within the first month of treatment. Both patients have also demonstrated symptomatic improvement. In a completed phase I and in ongoing phase I/II clinical trials, patients with treatment- ***refractory*** HER2/neu positive cancers (breast, ovarian, colorectal, prostate) have been treated with MDX-H210, which has been given alone and in conjunction with G-CSF, GM-CSF, and interferon gamma (IFN gamma). These trials have been open-label, progressive dose-escalation (0.35-135 mg/m2) studies in which single, and more often, multiple weekly doses have been administered. MDX-H210 has been well tolerated, with untoward effects being primarily mild-to-moderate flu-like symptoms. The MTD has not yet been defined. MDX-H210 is immunologically active, binding to circulating monocytes, causing monocytopenia, as well as stimulating increases in plasma cytokine levels. Furthermore, some patients have evidence of active antitumor immunity following treatment with MDX-210. Antitumor effects have been seen in response to MDX-H210 administration; these include 1 partial, 2 minor, and 1 mixed tumor response; 15 protocol-defined stable disease responses have occurred. (ABSTRACT TRUNCATED)

L4 ANSWER 44 OF 48 MEDLINE on STN DUPLICATE 34
ACCESSION NUMBER: 97118919 MEDLINE
DOCUMENT NUMBER: 97118919 PubMed ID: 8959761
TITLE: Impact of receptor downregulation on clearance of two human EGFs with different receptor binding activity.
AUTHOR: Sizemore N; Wright D S; Mueller W T; Kuo B S
CORPORATE SOURCE: Department of Pharmacokinetics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, USA.
SOURCE: PEPTIDES, (1996) 17 (7) 1229-36.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 20000303
Entered Medline: 19970314
AB Human epidermal growth factor [hEGF(1-53)] has been thought to be cleared mainly via an EGF receptor (***EGFR***) endocytosis pathway. Pretreatment of rats with hEGF(1-53) has been shown previously to cause a dramatic reduction in clearance of the peptide contributable to ***EGFR*** downregulation. The impact of receptor downregulation has raised concerns for rational design of dosage regimen for this potential wound-healing therapeutic peptide. However, following a similar protocol, we could not reproduce the dramatic reduction in clearance reported previously mediated by an i.v. bolus acute dose. As ***EGFR*** downregulation may be sensitive to the length of exposure and to the activation of the receptor tyrosine kinase activity, two other pretreatment protocols were also evaluated: a 4-h i.v. infusion (prolonged

exposure) of the peptide and an i.v. bolus of a potent synthetic kinase inhibitor pretreatment were evaluated for effects on clearance. However, neither pretreatment affected the peptide's clearance profile. Further, no effects on clearance and other kinetic parameters were observed for any pretreatment paradigms with a truncated analogue hEGF (1-48), whose EGF receptor binding activity is much weaker but plasma clearance is much higher than hEGF (1-53). In addition, a study in a second rat strain showed no difference in clearance profile of hEGF-(1-53) following pretreatment. Results of the present investigation suggest that receptor binding does not have a direct relationship with plasma clearance, and that the EGF clearance mechanisms is highly ***refractory*** with EGF receptors possibly recovering rapidly from downregulation through the recycling process.

L4 ANSWER 45 OF 48 MEDLINE on STN DUPLICATE 35
ACCESSION NUMBER: 1999034846 MEDLINE
DOCUMENT NUMBER: 99034846 PubMed ID: 9816014
TITLE: Changing pattern of expression of the epidermal growth factor receptor and transforming growth factor alpha in the progression of prostatic neoplasms.
AUTHOR: Scher H I; Sarkis A; Reuter V; Cohen D; Netto G; Petrylak D; Lianes P; Fuks Z; Mendelsohn J; Cordon-Cardo C
CORPORATE SOURCE: Genitourinary Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Cornell University Medical College, New York, NY 10021, USA.
CONTRACT NUMBER: CA-05826 (NCI)
CA-47538 (NCI)
DK-47650 (NIDDK)
SOURCE: CLINICAL CANCER RESEARCH, (1995 May) 1 (5) 545-50.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 20000303
Entered Medline: 19990208

AB The autocrine/paracrine interaction of the epidermal growth factor receptor (***EGFr***) and transforming growth factor alpha (TGF-alpha) has been implicated in prostate cancer cell growth and proliferation. To evaluate the role of ***EGFr*** and TGF-alpha in prostate cancer progression, we studied the immunohistochemical staining pattern of ***EGFr*** and TGF-alpha in malignant primary and hormone-independent metastatic prostate lesions. The specimens evaluated included 37 primary carcinomas (34 hormone-naive and 3 hormone- ***refractory*** tumors) and 22 metastases. For each specimen, the pattern of expression was evaluated and staining reactivities graded from 0-3, with 0 representing no staining and 3 representing homogeneous and intense staining. Primary malignant prostate epithelial cells in areas with discrete gland formation showed strong ***EGFr*** immunostaining, while stromal cells were generally nonreactive. In untreated primary tumors, TGF-alpha expression was primarily in the stroma, while epithelial cells were weakly positive in several cases. Malignant epithelial cells adjacent to neural elements that stained positive for TGF-alpha was frequently observed. A homogeneous staining pattern for ***EGFr*** was noted in 17 (89%) of 19 evaluable androgen-independent- ***refractory*** metastases, while TGF-alpha expression was found in 14 (78%) of 18 evaluable cases. Overall, 14 of 18 androgen-independent metastases coexpressed the receptor and the ligand. These results suggest that, unlike primary prostate tumors where a paracrine relationship between ***EGFr*** and TGF-alpha appears to predominate, the potential for autocrine stimulation may exist in the majority of metastatic androgen-independent tumors. Furthermore, the changing pattern of expression as the disease evolves from the localized hormone-naive to metastatic androgen-independent condition suggests that strategies aimed at blocking this growth factor pathway may be of therapeutic importance for androgen-independent disease.

L4 ANSWER 46 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:199552 BIOSIS
DOCUMENT NUMBER: PREV199598213852
TITLE: Epidermal growth factor receptor (***EGFr***) and TAG-72 expression in hormone ***refractory*** (HR) patients with locally recurrent and metastatic prostate (PR) cancer.
AUTHOR(S): Theodoulou, Maria; Reuter, Victor; Drobnjak, Maria; Kelly, Kevin; Scher, Howard I.
CORPORATE SOURCE: New York, NY, USA
SOURCE: Journal of Urology, (1995) Vol. 153, No. 4 SUPPL., pp. 450A.
Meeting Info.: Ninetieth Annual Meeting of the American Urological Association. Las Vegas, Nevada, USA. April 23-28, 1995.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 May 1995
Last Updated on STN: 5 May 1995

L4 ANSWER 47 OF 48 MEDLINE on STN
ACCESSION NUMBER: 92360652 MEDLINE
DOCUMENT NUMBER: 92360652 PubMed ID: 1498162
TITLE: Immunotherapy and monoclonal antibody therapies.
AUTHOR: Schuster J M; Bigner D D
CORPORATE SOURCE: Duke University Medical Center, Durham, North Carolina.
CONTRACT NUMBER: CA 11898 (NCI)
CA 56115 (NCI)
NS 20023 (NINDS)
SOURCE: CURRENT OPINION IN ONCOLOGY, (1992 Jun) 4 (3) 547-52. Ref: 31
Journal code: 9007265. ISSN: 1040-8746.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920925
Last Updated on STN: 20000303
Entered Medline: 19920915
AB High-grade malignancies of the central nervous system continue to be ***refractory*** to multimodality therapy. Immunotherapy with monoclonal antibodies, biologic response modifiers (eg, interleukin-2), and autologous, activated lymphocytes offer the potential for more selective therapy. Current research is likely to help overcome obstacles inherent in current monoclonal antibody therapy, including cross-reactivity with normal tissues, impermeability of the blood-brain barrier, and immunogenicity of murine-derived monoclonal antibodies. Treatment with adoptive cellular therapy and biologic response modifiers has been limited by low killing activity and specificity of the activated lymphocytes, limited infiltration of implanted cells, and the toxicity associated with systemically administered biologic response modifiers. Improved specificity and killing efficacy of activated lymphocytes will allow integration of cellular immunotherapy into the treatment of central nervous system malignancies.

L4 ANSWER 48 OF 48 MEDLINE on STN DUPLICATE 36
ACCESSION NUMBER: 84111792 MEDLINE
DOCUMENT NUMBER: 84111792 PubMed ID: 6319433
TITLE: A rapid decrease in epidermal growth factor-binding capacity accompanies the terminal differentiation of mouse

myoblasts in vitro.

AUTHOR: Lim R W; Hauschka S D

CONTRACT NUMBER: AM-18860 (NIADDK)
SOURCE: JOURNAL OF CELL BIOLOGY, (1984 Feb) 98 (2) 739-47.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198403
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 20000303
Entered Medline: 19840319

AB Specific mitogens stimulate the proliferation and repress the differentiation of mouse myoblasts (MM14). When mitogens are depleted, MM14 cells cease proliferation, commit to terminal differentiation, and become ***refractory*** to growth stimulation. The behavior of mitogen receptors during the transition from a proliferative to a permanently postmitotic state was examined using the epidermal growth factor receptor (***EGFR***) as a model system. Whereas proliferating myoblasts bound substantial amounts of EGF, their binding capacity declined rapidly upon exposure to low-mitogen medium. The decline became irreversible when a cell differentiated. Within 24 h, less than 5% of the original EGF binding capacity remained. Since the ability to internalize and degrade bound EGF was unaffected, the change presumably reflected a decrease in ***EGFR*** availability. Several observations indicated that loss of ***EGFR*** following mitogen removal is related to differentiation rather than the result of starvation or cell-cycle arrest. First, the decline is correlated with the absence of a single mitogen (fibroblast growth factor) and is independent of serum concentrations. Second, myoblasts that are either cycling through G1 or arrested at G0, but prevented from differentiating, all bind large amounts of EGF. These findings suggest that specific reduction in mitogen receptors could be part of a mechanism whereby terminally differentiating cells become ***refractory*** to mitogenic stimulation.